

REMARKS/ARGUMENTS

In response to the Office Action of November 25, 2003, Applicants request re-examination and reconsideration of this application for patent pursuant to 35 U.S.C. 132.

Claim Status/Support for Amendments

Claims 1, 39, 40 and 44-46 have been amended. Claims 2-38 were cancelled in a previous response (filed on August 21, 2003). Claims 39-46 are withdrawn from consideration. It is understood that claims 39-46, drawn to the non-elected invention, will remain pending, albeit withdrawn from prosecution on the merits at this time. If the examined claim of the Group I invention is deemed to be allowable, rejoinder of the remaining claims (39-46) in accordance with the decision in *In re Ochiai* is respectfully requested; since the remaining claims (39-46) are limited to the use of the biopolymer marker of claim 1 (the examined claim of the elected Group I invention).

Claim 1 is currently under examination. Claims 1 and 39-46 remain pending in the instant application.

No new matter has been added by the amendments to the specification made herein.

The title of the invention has been amended to correct an error in punctuation (Alzheimer's replaced Alzheimers).

In the "Background of the Invention" section a punctuation error was corrected at page 1, line 23.

The description of the reference at page 5 has been amended to correct a typographical error in the international application number. The corresponding international publication number has also been added.

The "Description of the Figures" section has been amended to correct an error in punctuation (Alzheimer's replaced Alzheimers).

Several protocols at pages 41-44 have been amended to properly identify trademark names (TRITON, TRIS and EPPENDORF). The protocol titles at page 41 (lines 2 and 16), page 42 (lines 8 and 22) and page 43 (line 12) were underlined in the original disclosure and do not indicate text amended herein.

The paragraph beginning at page 45 was amended to correct errors in grammar and punctuation.

In the "Detailed Description" section, the term "cerebrospinal fluid" has been added to define the abbreviation "CSF" at page 49, line 4 in order to provide additional support for cerebrospinal fluid as recited in claim 41. "CSF" is a well known abbreviation for cerebrospinal fluid in the biochemical art. Kits for determining the presence of the claimed biopolymer marker are discussed at page 47, lines 2-19; cerebrospinal fluid is noted to be one type of sample which can be used in the kit. A typographical

error within the same paragraph has also been amended (skill replaced skilled).

No new matter has been added by the amendments to the claims made herein.

Claim 1 has been amended to explicitly claim the biopolymer marker (amino acid residues 2-18 of SEQ ID NO:1). The term "biopolymer marker" is used throughout the specification as originally filed, see, for example, page 1, line 8.

Claim 39 has been amended to clearly disclose the relationship between the presence of the claimed biopolymer marker (amino acid residues 2-18 of SEQ ID NO:1) and Alzheimer's disease. Claim 39 has also been amended to explicitly indicate how the presence of the claimed biopolymer marker is determined from mass spectrum profiles. The changes to claim 39 find basis throughout the specification as originally filed, see, for example, page 35, lines 14-18, page 45, line 23 to page 46, line 6 and Figure 1.

Claim 40 has been amended to provide proper antecedent basis for the term "sample".

Claim 44 has been amended to correspond with the biopolymer marker of claim 1 (as amended herein). Support for various types of kits can be found in the original disclosure, see for example, page 36, lines 9-12 and page 47, line 2 to page 48, line 11.

Claims 45 and 46 have been amended to provide proper

antecedent basis for the term "kit" in claim 44 (as amended herein).

Oath/Declaration

A new declaration, which has been properly executed and dated, is filed herewith because while the original oath filed on March 8, 2002 contains the signature of Dr. John Marshall (inventor 2), the date of signature was omitted.

Restriction

The Examiner has withdrawn claims 39-46 from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention(s), there being no allowable generic or linking claim.

Request for Rejoining of Claims

Considering that claims 39-46 are limited to the use of an isolated biopolymer marker consisting of amino acid residues 2-18 of SEQ ID NO:1, a search of these claims would encompass this specific biopolymer marker. The instant application is related in claim format to several other applications, both pending and issued, of which serial number 09/846,352 is exemplary. In an effort to maintain equivalent scope in all of these applications,

Applicants respectfully request that the Examiner consider rejoining claims 39-46 in the instant application, which are currently drawn to non-elected inventions, under the decision in *In re Ochiai* (MPEP 2116.01) with claims (claim 1) of the elected invention, upon the Examiner's determination that the claim of the elected invention is allowable and in light of the overlapping search. If the biopolymer marker consisting of amino acid residues 2-18 of SEQ ID NO:1 is found to be novel, methods and kits limited to its use should also be found novel.

Rejection under 35 USC 112, first paragraph

Claim 1, as presented on August 21, 2003, remains rejected under 35 USC 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Examiner continues to maintain the position that the instant specification, as filed, fails to provide any evidence or sound scientific reasoning that would support the conclusion that the presence of an isolated peptide consisting of amino acid residues 2-18 of SEQ ID NO:1 in a sample would provide diagnosis of Alzheimer's disease.

Applicants respectfully disagree with the Examiner's position.

Although Applicants believe that the instant specification, as originally filed, fully supports the claim that an isolated peptide consisting of amino acid residues 2-18 of SEQ ID NO:1 is diagnostic for Alzheimer's disease, in the interest of compact, efficient prosecution, Applicants have removed the term "diagnostic" from the claims and note that the isolated peptide consisting of amino acid residues 2-18 of SEQ ID NO:1 is linked to Alzheimer's disease.

According to the web site, dictionary.com, the term "linked" refers to the condition of being associated with or connected to (see attached document as accessed from the internet; reference 1). The instant specification fully supports a connection and/or an association of the claimed peptide with Alzheimer's disease. The instant specification states at page 35, lines 14-18 that an objective of the invention is to evaluate samples containing a plurality of biopolymers for the presence of disease specific biopolymer marker sequences which evidence a link to at least one specific disease state.

The "test of enablement" is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the prior art without undue experimentation (see MPEP 2164.01).

Furthermore, the decision in *In re Brandstadter* (179 USPQ 286; MPEP 2164.05) has established that the evidence provided by applicant (to overcome an enablement rejection) need not be conclusive but merely convincing to one of skill in the art.

Applicants respectfully submit that the instant specification provides sufficient evidence to convince one of skill in the art that the claimed peptide (amino acid residues 2-18 of SEQ ID NO:1) is linked and/or associated with Alzheimer's disease.

Claim 1 has been amended to specifically recite an isolated peptide consisting of amino acid residues 2-18 of SEQ ID NO:1, a peptide which the instant specification identifies as related to Alzheimer's disease. Claim 1, as amended herein, does not recite that the claimed isolated peptide is diagnostic for Alzheimer's disease, nor does it recite that the claimed isolated peptide is related to Alzheimer's disease, even though Applicants believe that the specification, as originally filed, fully supports both of these recitations. Furthermore, the phrase "consisting of" is closed language and excludes any element, step or ingredient not specified in the claims (see MPEP 2111.03). Thus, the scope of claim 1 is limited to this specific peptide.

The gel shown in Figure 1 evidences that the biopolymer marker (amino acid residues 2-18 of SEQ ID NO:1) is present in samples of body fluid obtained from Alzheimer's patients, but is not present

in samples of body fluid obtained from patients who were age matched with the Alzheimer's patients (controls). Thus, a difference is seen between two comparable samples, suggesting that the differentially expressed peptide is linked to Alzheimer's disease.

The Examiner maintains that the specification does not provide a precise protocol on how to analyze the data obtained by the disclosed protocol.

Applicants respectfully disagree with the Examiner's position.

The specification, as originally filed, does provide a precise protocol on how to analyze the data obtained from the disclosed method. Page 25, line 16 to page 26, line 2 of the instant specification discloses a general outline of how to carry out the disclosed methods. Page 26, lines 6-13 of the instant specification further describes how samples were compared to develop data and indicates how biopolymer marker peptides were selected as notable sequences. This passage of the instant specification also discloses how certain peptides were selected from a plurality of molecules found within a sample and how peptides were deemed evidentiary of a disease state. Page 5, lines 12-20 also describes how biopolymer markers are evaluated according to the methods of the instant invention. Page 46, lines 14-16 of the instant specification clearly states the steps of the invention include obtaining a

sample from a patient and conducting an MS analysis (mass spectrometry) on the sample. Mass spectrometry is commonly practiced and one of skill in the art would know how to analyze and obtain information from mass spectrometry profiles. It is clear that the data presented in the instant specification was obtained by carrying out mass spectrometry. Thus, Applicants assert that the specification, as originally filed, provides a precise protocol on how to analyze the data obtained by the disclosed protocol.

Additionally, Applicants respectfully submit that such protocols are common practice in the field of proteomics.

For example, Scott D. Patterson presents the state of the art in mass spectrometry/proteomics by summarizing the Asilomar Conference on Mass Spectrometry (see attached article Physiological Genomics 2:59-65 2000; reference 2). This conference took place in 2000, thus coinciding with the time that the instant inventors were working to develop the instant invention.

In the disclosed method of the instant invention, proteins (as seen on a gel) that are identified as differentially expressed between a disease and a non-disease state are selected for excision (from the gel) and identification (see, for example, page 38, lines 3-7 of the instant specification as originally filed, and Figure 1). Such selection methods are common practice in the search for biomarkers of specific physiological states. For example, at page

61, right column of Patterson, several automation processes are discussed in the section titled "Automated identification of gel-separated proteins by mass spectrometry". This discussion begins with the following statement:

"Following quantitative analysis of 2-DE patterns, the next step is the identification of all protein spots that display differential expression."

Thus, it is concluded that it is common practice to select potential disease markers by their differential expression between a disease and a non-disease state.

Furthermore, Applicants respectfully submit that many of the methods disclosed in the instant specification are routinely practiced by those of ordinary skill in the art also attempting to identify biomarkers of particular physiological states.

For example, at page 64, left column of Patterson is a description of the SELDI approach (as discussed at the conference by Scot Weinberger) wherein defined chemical/biochemical surfaces are utilized to allow fractionation of proteins from biological fluids in a reproducible manner. This reproducibility allows comparisons between different samples to be made. Weinberger described a search for markers of benign prostate hyperplasia that, like prostate cancer, displays elevated prostate specific antigen (PSA) levels. The fraction exhibiting a difference between these

samples was able to be enzymatically digested, and a number of peptides were generated. These peptides were able to be fragmented using the MALDI-Qq-TOF (a procedure described by Ken Standing at the conference, page 62, left column of Patterson). It was found that there appears to be a difference in the relative level of seminogelin fragments between these two states (prostate cancer and benign prostatic hyperplasia), thus providing a potential differential marker.

Applicants respectfully draw the Examiner's attention to the fact that the method described by Weinberger is analogous to the method described in the instant specification. Furthermore, when interpreting data Weinberger uses the same approach to interpretation as the instant inventors in order to identify seminogelin fragments as a potential marker to distinguish between benign prostate hyperplasia and prostate cancer based on differential expression of the fragments. Additionally, Applicants respectfully point out to the Examiner that Weinberger linked differential expression of seminogelin to benign prostate hyperplasia and prostate cancer without analysis of a sample from a control patient free of disease or analysis of a sample from a patient having another disease, which is not benign prostate hyperplasia or prostate cancer. Such linking of markers with disease through differential expression is commonly practiced in

proteomics.

Furthermore, Applicants assert that those of skill in the art are both highly knowledgeable and skilled and it is obvious that no undue experimentation would be required for a skilled artisan to follow any of the electrophoretic, chromatographic and mass spectrometric protocols presented in the instant specification in order to use the claimed invention. One of skill in the art would be able to view a gel, such as that shown in Figure 1 from which the claimed peptide was identified (amino acid residues 2-18 of SEQ ID NO:1), and recognize a difference between two comparable samples (disease state vs. non-disease state) and further recognize that the peptides present within the gel are differentially expressed between the two sample types.

The Examiner further asserts that the instant specification fails to present any description of samples used in the experiments to determine the presence or absence of the claimed marker.

Applicants respectfully disagree with the Examiner's assertion.

The exemplary preparatory protocols which can be used to carry out the methods of the invention clearly indicate that the samples used are samples of sera, for example, see step 3 of the DEAE column protocol at page 41. However, other body fluids can also be used, see page 52, lines 12-19. These samples are obtained from a

human patient, see page 46, lines 14-16 of the instant specification. The lanes of the gel shown in Figure 1 are clearly labeled with patient numbers that indicate if the sample shown in each lane is obtained from an Alzheimer's patient (lane 1, ADH-004, for example), a patient age matched with an Alzheimer's patient (lane 6, ADC(H)-003, for example) or a sample pooled from a plurality of normal patients (lane 9, pooled NHS). Thus, contrary to the Examiner's assertion, the instant specification describes the samples used in the experiments disclosed therein.

The data presented in Figure 1, derived from the working examples, discloses that the claimed peptide (amino acid residues 2-18 of SEQ ID NO:1) is differentially expressed between Alzheimer's disease and a physiological state age matched with Alzheimer's disease, thus it can be reasonably predicted that such peptide is linked to Alzheimer's disease. Furthermore, Figure 1 identifies SEQ ID NO:1 and the specification discloses how such a sequence was identified as a notable sequence in relation to Alzheimer's disease.

Thus, based upon the above comments, Applicants contend that a skilled practitioner would find that the data presented in the instant specification is convincing with regard to a link between the claimed biopolymer marker peptide (amino acid residues 2-18 of SEQ ID NO:1) and Alzheimer's disease.

Considering the above comments, it is clear that both the specification and the prior art disclose how to make and use the instant invention. Accordingly, Applicants respectfully contend that the instant invention satisfies the "test for enablement" since one skilled in the art could make or use the invention from the disclosures in the specification coupled with information known in the prior art without undue experimentation.

The Examiner makes several assertions regarding the enablement of subject matter which is not claimed, including the assertion that the instant specification does not present information regarding presence or absence of the instant peptide (amino acid residues 2-18 of SEQ ID NO:1) in serum samples of pathological conditions other than Alzheimer's disease, or serum samples of patients suspected of having Alzheimer's disease, in which such marker would be present, followed up by a diagnosis of AD using other diagnostic methods.

The Examiner is reminded that all questions of enablement should be evaluated against the claimed subject matter and the focus of the examination inquiry should be a question of whether everything within the scope of the claims is enabled (see MPEP 2164.08).

Accordingly, an Applicant is not required to enable material which is not claimed. The pending claims do not recite that the

claimed peptide is diagnostic for any pathological condition, including Alzheimer's disease. Thus, no teachings regarding diagnostics are necessary in order to provide evidence for enablement of the pending claims. However, even if the pending claims were drawn to diagnostics, Applicants respectfully submit that such claims would be enabled without analysis of a sample from a control patient free of disease or analysis of a sample from a patient having another pathological condition; since, linking of markers with a disease by differential expression of peptides alone is commonly practiced (see above discussion of the Weinburger study).

Additionally, Applicants assert that the intended purpose of the invention is to provide improved, alternative means for diagnosis of Alzheimer's disease which can easily be performed by an untrained individual without the need for additional testing. If "follow-up" diagnostic methods are required, then the diagnostic process is lengthened and the invention fails to fulfill its intended purpose.

The guidelines for a "test of enablement" indicate that if a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 USC 112, is satisfied (see MPEP 2164.01(c)).

Applicants assert that amino acid residues 2-18 of SEQ ID NO:2 is linked to Alzheimer's disease, however, do not claim that such sequence is a unique marker for any particular disease or condition.

Although the prior art does not specifically recognize that the claimed marker (amino acid residues 2-18 of SEQ ID NO:1), a fragment of the plasma protease C1 inhibitor precursor protein, is related to Alzheimer's disease, it does recognize that when a peptide is identified in a body fluid sample from an Alzheimer's patient or appears to be differentially expressed between an Alzheimer's disease patient and a "normal" patient, it is immediately recognized as a potential diagnostic marker, even if the involvement of the peptide in the pathology of Alzheimer's disease is unknown. One of skill in the art would be familiar with this practice since it has been known in the art since at least 1992. See attached abstract of Gunnarsen et al. (Proceedings of the National Academy of Science USA 89(24):11949-11953 1992; reference 3) in which the detection of glutamine synthetase in the cerebrospinal fluid of Alzheimer's disease patients lead to the suggestion of glutamine synthetase as a potential diagnostic biochemical marker for Alzheimer's disease. When one of skill in the art observes differential expression of the claimed peptide between Alzheimer's disease patients and non-diseased patients; one

of skill in the art would connect this peptide with potential diagnostic and/or therapeutics for Alzheimer's disease.

Thus, Applicants respectfully submit that since the specification demonstrates a link between the claimed peptide (amino acid residues 2-18 of SEQ ID NO:1) and Alzheimer's disease and that this link connotes the use of the claimed peptide in potential diagnostics and/or therapeutics of Alzheimer's disease, the requirement of "how to use" under 35 USC 122, first paragraph is satisfied.

Furthermore, Applicants respectfully submit that one of ordinary skill in the art would find the suggestion of a link between the claimed peptide (amino acid residues 2-18 of SEQ ID NO:1) and Alzheimer's disease to be reasonable.

The C1 inhibitor protein is a regulatory molecule that inhibits complement C1 activity (see attached definition of C1 INH, as accessed from the internet at "immunoglossary"; reference 4), thus controlling the inflammatory complement cascade (see attached abstract of Walker et al. Brain Research 675(1-2):75-82 1995; reference 5). At page 46 of the instant specification as originally filed, the claimed biopolymer marker (amino acid residues 2-18 of SEQ ID NO:1) is identified as a fragment of a C1 inhibitor protein. The instant inventors found that this peptide (amino acid residues 2-18 of SEQ ID NO:1) was present in samples of body fluids obtained

from Alzheimer's disease patients (see Figure 1).

Activation of the classical complement pathway and up-regulation of its protein components in Alzheimer's disease has been documented in the art (see attached abstract of Yasojima et al. American Journal of Pathology 154(3):927-936 1999; reference 6). Additionally, the complement C1 inhibitor is known to be cleaved in Alzheimer's disease and has been found to be present in abnormal neuronal processes in Alzheimer's tissue (see attached abstract of Walker et al. Brain Research 675(1-2):75-82 1995; reference 5).

One of ordinary skill in the art would be aware of the involvement of the complement system in the pathology of Alzheimer's disease. Therefore, one of ordinary skill in the art would recognize the linkage between the claimed peptide (amino acid residues 2-18 of SEQ ID NO:1); complement C1 inhibitor; and the activation of complement in Alzheimer's disease and thus would also find the suggestion of the claimed peptide (amino acid residues 2-18 of SEQ ID NO:1) as a marker for Alzheimer's disease entirely reasonable. The Examiner is reminded that evidence presented by applicant to provide enablement of an invention need only be convincing to one of skill in the art and not conclusive (see MPEP 2164.05).

The Examiner asserts that the Declaration of Lander under 37

CFR 1.132 filed on August 21, 2003 is insufficient to overcome the rejection of claim 1.

Applicants respectfully disagree with the Examiner's assertion.

The Examiner further asserts that the Declaration provides additional data obtained by MS analysis regarding the absence of the claimed peptide in normal sera as compared to sera from patients with Alzheimer's disease.

Applicants respectfully contend that this assertion of the Examiner is incorrect. The Declaration provides information compiled from data obtained from the original experiments and does not contain any additional data or new data obtained after the instant application was filed. Both the Declaration and the Response filed on August 21, 2003 note thus.

The figure attached to the Declaration compares two mass spectral profiles side-by-side; the top profile shows normal human sera and the bottom profile shows Alzheimer's sera. This profile comparison clearly evidences that the marker weighing 1826 daltons (the claimed marker) is absent from normal human sera and present in Alzheimer's sera; thus suggesting that the marker may be linked to Alzheimer's disease. These mass spectral profiles can be used as a reference point for identification of the claimed marker in unknown samples.

The Examiner cites an article, Clark et al. (see attached abstract Archives of Neurology 50(11):1164-1172 1993; reference 7), which is allegedly relevant to the instant invention. Clark et al. is deemed to teach that a definite diagnosis of Alzheimer's disease requires pathological confirmation on autopsy. Apparently, the Examiner believes that since Clark et al. teach pathological confirmation on autopsy is necessary for a definite diagnosis of Alzheimer's disease no other methods are of value.

The guidelines for a "test of enablement" indicate that if a statement of utility in the specification contains within it a connotation of how to use, 35 USC 112 is satisfied. Applicants claim that the presence of a biopolymer marker peptide (amino acid residues 2-18 of SEQ ID NO:1) is linked to Alzheimer's disease; a statement which is enabled by the data presented in Figures 1. The claimed method involves a simple observation of the presence of the marker (as shown in Figure 1) in a gel, and conducting mass spectrometry analysis to identify the markers present in the gel.

Hampel et al. (Journal of Neural Transmission 111:247-272 2004; reference 8) disclose a study similar to that of the instant inventors; see page 260, last paragraph. In this study the content of body fluid obtained from MCI (mild cognitive impairment) patients was compared with the content of body fluid obtained from normal control patients. The MCI patients showed an elevated level

of a protein, p-tau₂₃₁, in comparison to the healthy control patients. Hampel et al. deemed the results of this study adequate to suggest that high levels of p-tau₂₃₁ may be a predictor for progressive cognitive decline in subjects with MCI. This disclosure of Hampel et al. demonstrates further that when elevated levels of proteins are found associated with a disease state, the protein is considered useful for potential diagnostics and/or therapeutics in the disease condition. When subjected to the "test for enablement" the Examiner's argument is not sufficient to support the enablement rejection; since the association of the claimed biopolymer marker (amino acid residues 2-18 of SEQ ID NO:1) with Alzheimer's disease carries with it a connotation of use for diagnostics.

Furthermore, the Examiner is reminded that the mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it (MPEP 2164.02).

The conventional "definitive diagnosis" does not control the usefulness of other methods suggested for diagnosis. Diagnostic methods other than postmortem examination and brain biopsy have been deemed valuable for diagnosing Alzheimer's disease. For example, Applicants submit their own patent, US 6,451,547 B1 (Jackowski et al.; reference 9) which claims methods for diagnosing Alzheimer's disease by detecting the presence of biochemical

markers in bodily fluid.

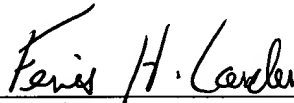
Thus, Applicants respectfully submit that the teachings of Clark et al. have no relevance with regard to the instant invention.

In conclusion, Applicants claim that the differential expression of amino acid residues 2-18 of SEQ ID NO:1 (present in Alzheimer's disease; absent in age matched control) between Alzheimer's patients and patients age matched with the Alzheimer's patients evidences a link between the claimed peptide (amino acid residues 2-18 of SEQ ID NO:1) and Alzheimer's disease; a statement which is enabled by the instant specification, as evidenced by the arguments presented herein. Applicants assert that one of ordinary skill in the art, when reviewing the instant specification, given the level of knowledge and skill in the art, would recognize the link between the claimed biopolymer marker (amino acid residues 2-18 of SEQ ID NO:1) and Alzheimer's disease and would further recognize how to use the claimed sequence as a marker for Alzheimer's disease. Thus, Applicants respectfully request that this rejection under 35 USC, 112, first paragraph now be withdrawn.

CONCLUSION

In light of the foregoing remarks, amendments to the specification and amendments to the claims, it is respectfully submitted that the Examiner will now find the claims of the application allowable. Favorable reconsideration of the application is courteously requested.

Respectfully submitted,



Ferris H. Lander
Registration # 43,377

McHale & Slavin, P.A.
2855 PGA Boulevard
Palm Beach Gardens, FL 33410
(561) 625-6575 (Voice)
(561) 625-6572 (Fax)

\\Ns2\SERVER\CLIENT FILES\2100-2199\2132 -Syn-X\2132_000086 - Plasma Protease C1
Biopolymer\Amendments\2132_086_AM2.wpd